INTRODUCTION
A CT scan of the brain is an indispensable component of the clinical assessment of patients with acute stroke. It rapidly demonstrates stroke-mimicking conditions, and – within the first week of stroke – is still the best way to differentiate haemorrhage from infarct. However, the old view that the CT was essentially normal in ischaemic stroke is no longer valid. Subtle, early signs of infarction have been identified, which help to confirm the diagnosis and may guide treatment. In this review, we will discuss some of the factors that influence the appearance of the CT scan in acute stroke. We will describe the early signs of infarction, what they mean, and areas of uncertainty that require more study. We will highlight some of the limitations of CT scanning, suggest clinical situations where MR may be appropriate, and what sequences should be requested.

Figure 1 A 51-year-old-man with left sided weakness and drowsiness. CT (3 h 38 mins from onset) shows a large haemorrhage in the right basal ganglia (arrow), with extension into the right lateral ventricle and midline shift.

NEUROIMAGING
CT for acute ischaemic stroke

In 2001, and for the foreseeable future, CT is the brain imaging modality of choice in suspected acute stroke (Ketonen & Berg 1997; Wardlaw 2001; Buchan 2001; von Kummer & Patel 1999). It is widely available: 92% of consultants caring for patients with stroke in the UK have access to a CT scanner (Ebrahim & Redfern 1999). An unenhanced CT scan of the brain (5 mm slices through the posterior fossa, 10 mm slices throughout the rest of the brain) takes only 5 min. Fast CT provides diagnostic information even in restless, uncooperative patients, and allows access to critically ill patients during scanning.

The evaluation of a patient with suspected stroke is incomplete without a CT brain scan. The first diagnostic step is to distinguish between a vascular and a nonvascular lesion. Stroke-mimicking conditions such as subdural haematoma, abscess, or brain tumour (which are the underlying lesions in about 4% of patients presenting with a stroke syndrome) can usually be distinguished from a vascular lesion by a combination of clinical assessment and CT scan (Kothari et al. 1995; Weisberg & Nice 1977).

After excluding a nonvascular cause, the major reason for performing a CT brain scan is to differentiate haemorrhage from infarct. This cannot be done reliably by clinical examination alone. All haemorrhages large enough to cause symptoms will be seen (Wardlaw 2001), and are visible as soon as blood stops moving (Franke et al. 1990). The CT appearance is of increased density (or whiteness) and is usually obvious (Fig. 1). Increased density on CT is a result of
both the haemoglobin content and the protein matrix of the clotted blood. Haemorrhages are visible in patients with anaemia, thrombocytopenia or abnormal clotting syndromes (Pierce et al. 1994). The haematoma gradually loses its hyperdensity – the whiteness disappearing as the haematoma is broken down. After a few weeks – depending on the size of the haematoma – it can appear identical to an infarct of the same age (Dennis et al. 1987).

WHAT INFLUENCES THE LIKELIHOOD OF SEEING AN INFARCT ON CT?

In the past, CT was thought to be insensitive to ischaemic changes in the first 24 h (Wardlaw et al. 1999). Even now, an infarct may never be seen in up to 50% of patients (Wardlaw 2001). Signs of infarction on CT within the first six hours of stroke are often subtle [Fig. 2(a), and see below] but become more obvious and better demarcated over the first few days [Fig. 2(b)]. When visible, an established infarct (i.e. one that is a day or so old) appears as a wedge-shaped or rounded hypodensity within a recognized vascular territory. Swelling may be seen within the lesion, reaching its peak around the third to fifth day.

The likelihood of seeing a relevant infarct depends on time to scanning, and stroke severity. The later a patient is scanned, and the more extensive the clinical syndrome, the greater the chance of seeing an infarct. In the International Stroke Trial (IST) (IST Collaborative Group 1997), of the 12 802 patients randomised immediately after CT, an infarct was visible in 50%. An infarct was seen in 33% of patients scanned within 6 h, and in 58% of those scanned 24–48 h after onset. Overall, 61% with an extensive clinical syndrome (total anterior circulation infarct) had a visible infarct, compared with 41% of those with lacunar clinical syndromes. The interaction between time and severity in the IST is illustrated in Fig. 3. There is a weak independent association of visible infarction with poor outcome – a patient with a visible infarct has a slightly worse prognosis than an otherwise identical patient with no visible infarct (Wardlaw et al. 1998).

WHEN SHOULD INTRAVENOUS CONTRAST BE USED?

Administration of intravenous contrast has limited value and should be avoided except in specific circumstances (Beauchamp et al. 1997). Contrast does little to alter the appearance of an infarct when given in the first few days, but following that, marked enhancement may be seen. This radiological appearance is often termed ‘luxury perfusion’ and reflects blood-brain barrier breakdown, neovascularization and impaired autoregulation (Fig. 4). ‘Luxury perfusion’ has occasionally been mistaken for a tumour or abscess, because of the ring-enhancing appearance (Ketonen & Berg 1997). Hence, a noncontrast CT should always be performed first in suspected stroke. Specific reasons for giving contrast might include obtaining perfusion or angiographic images, to look for an underlying arteriovenous malformation or tumour-causing intracerebral haemorrhage, or in the case of an odd-looking infarct, to exclude a tumour. However, it may still be necessary to re-
PEAT the scan a couple of weeks later, by which time an infarct will have shrunk but a tumour may have grown.

MAKING A POSITIVE DIAGNOSIS: EARLY CT SIGNS OF INFARCTION

With advances in modern CT technology, and more patients presenting for early assessment, signs of infarction may be seen on a scan within a few hours of stroke onset. Unfortunately, these signs are subtle and may be missed. The characteristic changes are a loss of tissue density, resulting in loss of distinction between grey and white matter, and swelling. The pathological process that explains these signs is an influx of water into affected ischaemic cells. The grey matter is affected first, as neurones are more sensitive to ischaemia than other cells (Beauchamp et al. 1997). It is worthwhile becoming familiar with these signs, if only to impress colleagues (and radiologists) at neuroradiology meetings!

The brief monograph from von Kummer and colleagues is highly recommended (von Kummer et al. 1995). A suggested approach to the evaluation of early signs of infarction is to look systematically at the scan for the typical changes, comparing parts of one hemisphere to the equivalent area in the other.

Hyperdense middle cerebral artery sign (HMCAS)

This is not strictly a sign of early infarction, but reflects occlusion of the middle cerebral artery (MCA) by acute thrombus or embolism (von Kummer et al. 1995). The CT appearance (Fig. 5) is an increased density of part of the MCA, compared with other parts of the vessel or its contralateral counterpart (and not attributable to calcification). Although most frequent in the MCA, any artery may appear hyperdense when it contains fresh thrombus (even the lenticulostriate arteries (Wardlaw et al. 2001)). In the distal MCA, it has been called the hyperdense sylvian fissure ‘dot’ sign (Barber et al. 2001) (Fig. 6).

Basal ganglia

Loss of definition of grey matter is most obvious at the interface of grey and white matter in the basal ganglia. The distinction between caudate nucleus and anterior limb of internal capsule, globus pallidus and genu of internal capsule, and putamen and external capsule, is blurred or lost (Fig. 6). Within the first few hours, the is-
chaemic grey matter becomes a similar density to the adjacent white matter. Later, the grey and white matter become even more hypodense, so that the whole area is darker than surrounding brain tissue. Swelling is seen as compression of the adjacent ventricle [Figs 2(b) and 7(b)].

Cortical surface
Swelling of the cortex results in effacement (loss of visibility) of the sulci in the territory of the involved artery, most easily seen by comparing sulci in corresponding parts of each hemisphere [Figs 2(a), 7(a) and 8(a)]. Loss of definition between grey and white matter may be seen at the boundary between cortex and white matter, in particular involving the insular cortex between the sylvian fissure and external capsule. Loss of definition of the insular cortex results in ‘loss of the insular ribbon’ [(Fig. 9(a)]. Subsequently both grey and white matter become hypodense, so more obviously abnormal.

How often do these changes occur?
Small studies in the early 1990s (in which it is unclear how patients were selected) reported that hypodensity and/or swelling were seen in 82% of patients with hemispheric stroke when scanned within 6 h (von Kummer et al. 1996). In the European Cooperative Acute Stroke Study (ECASS), patients were enrolled within 6 h of symptom onset (following CT scan). 46% had parenchymal hypodensity, and 21% had focal swelling on the initial scan (in the opinion of the expert CT reading panel, who were not blind to the follow-up scans) (von Kummer et al. 1995). Conversely, the NINDS rt-PA trial, in which patients were enrolled within three hours, had a low frequency of clear-cut early CT findings (5.7%) (von Kummer & Patel 1999).

The frequency of the HMCAS ranges from 50% in some series (Moonis & Fisher 2001; Bastianello et al. 1991; von Kummer et al. 1994) to 17.7% (Manelfe et al. 1999), and was only 5% in a recent Canadian study of patients eligible for intravenous thrombolysis (Barber et al. 2001). An equal number of patients may not demonstrate the HMCAS despite angiographically proven MCA occlusion (von Kummer et al. 1994; Leys et al. 1992). A hyperdense distal MCA is reported to occur in 16% of thrombolysis-eligible patients (Barber et al. 2001). When studied serially, the HMCAS usually disappears in a few days (Bastianello et al. 1991).

It is difficult to be certain of the true frequency of early signs of infarction. It all depends on the severity of stroke in the particular patient group, the size and position of the infarct, how quickly patients are scanned, the expertise of the radiologist, the quality of the scanner, and so on.

After excluding a nonvascular cause, the major reason for performing a CT brain scan is to differentiate haemorrhage from infarct...
Figure 7  (a) An 80-year-old-woman developed mild right sided weakness, then deteriorated 2.5 h later with dense weakness and aphasia. CT (50 mins after deterioration, 3 h 20 mins after onset) shows very subtle loss of grey-white differentiation in the anterior division of left middle cerebral artery (black arrow). (b) 48 h later there is an extensive established infarct (thin arrows) with compression of the lateral ventricle and petechial haemorrhagic transformation (thick arrow) within a larger island of surviving tissue. The patient died 3 months later.

Figure 8  (a) A 42-year-old man collapsed in court with headache and drowsiness. Noted to have a left hemiparesis. CT (9 h 15 mins from onset) shows loss of grey-white differentiation and sulcal effacement in the right frontal region, obscuration of the lentiform and caudate nuclei, and compression of the lateral ventricle on the right (black arrows; the normal is shown by white arrows). (b) At 24 h, MR diffusion weighted image showed extensive signal alteration in the right middle and anterior cerebral artery territories. The large white blob is far more obvious to the casual observer than the subtle changes seen on CT scan (a). Analysis of the MR angiogram and cross sectional images suggested a probable dissection of the right internal carotid artery, however, the appearances of dissection can be confusing. The patient died 80 h after onset due to 'malignant' middle cerebral artery infarction.
A study that reports high frequencies probably reflects the interests of the research group and the mix of patients admitted to its service, and may not be easily extrapolated to the rest of the world. Early signs of infarction, and the presence of visible clot in a large cerebral vessel, are helpful to confirm the clinical diagnosis when present, but their absence should not affect the diagnostic process—it could still be an ischaemic stroke.

UNRESOLVED ISSUES – LIMITATIONS OF EARLY CT SIGNS OF INFARCTION

Enthusiasm for making an early positive diagnosis on CT needs to be balanced by an understanding of the problems involved. Confusion has arisen through the use of multiple terms for early infarct signs that describe two basic pathological processes: ischaemia and swelling (Table 1) (Wardlaw 2001). In one study, 5/15 doctors even observed an invented sign (‘dense cortical sulci’) on CT, suggesting that knowledge of early infarct signs was poor (Wardlaw et al. 1999). There needs to be simplification, as well as clear and universally agreed definitions for early CT signs of infarction.

How reliable are early signs of infarction?

Even amongst neuroradiologists with an interest in stroke, agreement of early signs is moderate at best (Marks et al. 1999; Kalafut et al. 2000). There are not—and will probably never be—enough neuroradiologists to provide timely reports to clinicians (Brillman et al. 1997) (although in the future, use of image link technology may allow...
With advances in modern CT technology, and more patients presenting for early assessment, signs of infarction may be seen on a scan within a few hours of stroke onset.

One neuroradiologist to cover vast areas, even several countries. However, at present, clinicians must assess their own scans (particularly at unsociable hours), and may need to base treatment decisions on the CT scan. Unfortunately, the reliability amongst general radiologists, stroke clinicians and emergency physicians, so far for detecting early signs of infarction is poor, barely better than would be achieved by chance alone (Wardlaw et al. 1999; Kalafut et al. 2000; Barber et al. 2000; Grotta et al. 1999).

An even greater worry is that clinicians may not even detect haemorrhage reliably: 40% of neurologists (and only 17% of emergency physicians) correctly identified all haemorrhages in one study (Schriger et al. 1998). Better training of clinicians in reading scans might help, but such training should probably concentrate on getting the basics right – identification of haemorrhage – before attempting the more difficult signs of early infarction.

What does it all mean?

When seen in the proximal vessel, the HMCAS is associated with severe brain ischaemia and poor outcome, but has no independent prognostic significance (Manelfe et al. 1999). A distal HMCAS is associated with smaller volumes of infarcted tissue and better prognosis (Barber et al. 2001). Several studies have shown that early infarct signs have a strong univariate association with stroke severity and outcome (Moulin et al. 1996; von Kummer et al. 2001), but do not independently predict outcome in multivariate analyses (Mendizabal et al. 2001). It is likely that early infarct signs, as with established infarct signs, probably have a weak independent effect on prognosis. However, this and the magnitude of any independent association, is still to be determined.

Current thinking is that these early CT changes reflect the pathophysiology of the infarct (Buchan 2001; von Kummer & Weber 1997). Early evidence of infarction involving a large part of the cerebral hemisphere is thought to represent major, irreversible ischaemic damage, where reperfusion is unlikely to be helpful. When the CT changes are more subtle, positron emission studies (albeit of very small sample size) have suggested that there is a small core of tissue destined to infarct, surrounded by a larger area of critically hypoperfused (yet still viable) brain tissue (Grond et al. 1997). The current thinking is that reperfusion is likely to be of benefit in this situation, and that those with normal CT scans may recover rapidly, or develop delayed infarction (von Kummer & Hacke 2000). However, all of this conjecture remains to be proven.

Using early signs to select patients for treatments: the ‘1/3 rule’

The European Co-operative Acute Stroke Study (ECASS) attempted to select patients thought most likely to respond to thrombolytic therapy by excluding those with hypodensity of more than 1/3 of MCA territory (Hacke et al. 1995). This figure was chosen on evidence that hypodensity greater than 50% of MCA territory was associated with 85% mortality (von Kummer et al. 1994). The ECASS (Hacke et al. 1995) found that mortality was 13% in patients with a normal early scan, 23% in patients with hypodensity estimated to cover less than 1/3, and 49% in patients with hypodensity greater than 1/3 of MCA territory (von Kummer et al. 1995). However, the trial suffered from a high number of ‘protocol violators’ – 52 of 620 patients randomised had CT abnormalities that should have resulted in exclusion from the trial. Defining what constituted 1/3 or more of the MCA territory proved to be difficult, as it has in many other studies (Wardlaw et al. 1999; Kalafut et al. 2000; Grotta et al. 1999). In fact, there is no definition. Even the originators of the sign did not provide a definition. For a start, the extent of MCA territory varies between individuals, and even between hemispheres in the same individual (Bamford 2001). Despite the difficulty of basing treatment decisions (or eligibility for a trial) on an unreliable sign, numerous guidelines on the use of thrombolysis recommend avoiding treatment in patients with hypodensity > 1/3 of MCA territory (Anonymous 1996; Adams et al. 1996). Yet the one trial of thrombolysis that was positive did not have CT visible infarction as an exclusion criterion (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995), and the interaction between thrombolysis, visible infarction and outcome has never been determined.

There have been some recent attempts to improve reliability of early scan interpretation.
One study formalized the interpretation of the 1/3 rule (by applying a series of imagined templates) (Silver et al., 2001), and another developed a systematic quantitative scoring system for ischaemic changes in the MCA territory (ASPECTS) (Barber et al. 2000). Both studies report impressive interobserver reliability, but are based on small numbers of patients treated with intravenous thrombolysis. Neither scale can be used for the many infarcts that occur outside MCA territory. In the future, the safety and efficacy of acute ischaemic stroke treatments may be improved by selecting patients after careful assessment of the pretreatment CT (Buchan 2001), but there is still much work to be done to determine whether that is really the case.

WHEN TO ORDER AN MRI (AND WHAT SEQUENCES TO ASK FOR)

Magnetic resonance (MR) imaging has important limitations in stroke patients. Before ordering an MRI scan, it should be noted that scanning time is considerably longer than CT, it is noisy and images may be rendered uninterpretable by patient movement. Intra-ocular metallic foreign bodies, pacemakers or intracranial aneurysm clips are absolute contraindications. During the scan, the stroke patient – often at risk of aspiration, or confused and distressed – is not readily accessible (Wardlaw 2001). In the UK, few stroke clinicians have access to same or even next day MR scanning (Ebrahim & Redfern 1999).

An acute ischaemic stroke has characteristic features on MR imaging. Within minutes, loss of the normal flow void in the symptomatic artery may be seen (best on proton density sequences; Mead & Wardlaw 1998); by 3–6 h swelling will be evident, and by 8 h there will be brightness on T2-weighted images (Wardlaw 2001). Diffusion weighted MR imaging (DWI) is capable of demonstrating ischaemia within minutes of onset (as areas of brightness; Fig. 8b; Ketonen & Berg 1997; Fisher et al. 1992). However, evidence is emerging that a careful, systematic evaluation of the early CT is as good as MR with DWI in detecting acute ischaemia, at least in patients with moderate to severe strokes (Barber et al. 2001).

There are advantages of MR over CT in acute stroke. Particular clinical indications for MR, and the appropriate sequence to request, are listed in Table 2. Structural MR sequences demonstrate some infarcts better than CT, but MR can be confusing because it is sensitive but not specific (Hommel et al. 1995). Magnetic resonance angiography (or venography) can detect occlusions, abnormalities or stenoses of major intracranial and extracranial vessels (Ketonen & Berg 1997). The gradient echo sequence (GRE) is sensitive to the presence of intraparenchymal blood indefinitely (Fig. 10b) (Wardlaw 2001). DWI allows distinction between old and new infarcts (Fig. 11d), as the brightness of a recent infarct on DWI fades over a few weeks (Albers et al. 2000). Perfusion imaging detects reduced flow.

<table>
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<tr>
<th>Clinical Indication</th>
<th>MR sequence*</th>
<th>Special Notes</th>
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<tbody>
<tr>
<td>The ‘young’ patient</td>
<td>Structural images</td>
<td>Higher chance of rare cause of stroke – MR can aid diagnosis greatly (Warlow et al. et).</td>
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<tr>
<td>Suspected vasculitis, bacterial endocarditis</td>
<td>Structural images</td>
<td>May demonstrate multiple lesions</td>
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<tr>
<td>Posterior circulation stroke</td>
<td>Structural images, Diffusion weighted imaging</td>
<td>MR shows the posterior fossa better than CT (Beauchamp et al. et)</td>
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<td>Carotid or vertebral dissection</td>
<td>MRA of neck</td>
<td>Allows noninvasive angiography, however, catheter angiography may still be required (Warlow et al. et)</td>
</tr>
<tr>
<td>CADASIL, MELAS</td>
<td>Structural images</td>
<td>Characteristic changes on T2 weighted images</td>
</tr>
<tr>
<td>Venous infarction</td>
<td>Structural images, MR venogram</td>
<td>MR may be better than CT to identify venous infarction (Quint 2000)</td>
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<td>Patients presenting later than 2 weeks (Fig. 10)</td>
<td>Gradient echo</td>
<td>A normal CT does not rule out haemorrhage; if the detection of old haemorrhage is important should perform MR with Gradient echo sequence</td>
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<tr>
<td>Distinguishing old lesions from new (Fig. 11)</td>
<td>Diffusion weighted imaging</td>
<td>As long as recent event occurred within a few weeks of scanning</td>
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*MR sequence: structural images are T1- and T2-weighted images, proton density or fluid attenuated inversion recovery (FLAIR) sequences, performed as part of routine MR.
Figure 10  (a) A 62-year-old man presented with dizziness and unsteadiness. He had multiple vascular risk factors, and had an episode of right arm and leg weakness 6 months ago. CT brain 5 months ago showed a small hypodensity in the left basal ganglia (arrow). (b) Gradient echo MR performed on this admission shows that the lesion was a haemorrhage (thick arrow), with several additional areas of old punctate haemorrhage (thin arrows). Linear hypodensities like this on CT should raise the suspicion of old haemorrhage.

Figure 11  (a,b) A 46-year-old man, with a history of hypertension and a previous stroke causing right-sided sensory disturbance, developed further right-sided sensory alteration and mild weakness. CT (1 h 26 mins after onset) shows several low densities consistent with old lacunar infarcts (arrows). (c) MR T2 weighted images 30 min later shows many more lesions in the white matter (arrows). (d) The diffusion weighted MR sequence shows a high attenuation lesion in the appropriate hemisphere (arrow), suggesting this to be the infarct responsible for the recent clinical event.
blood flow to an area of brain. The current hope for hyperacute stroke is that combined DWI and perfusion imaging may indicate the presence of viable brain tissue — the ischaemic penumbra (Ketonen & Berg 1997; Wardlaw 2001). However, current data are limited (Powers 2000), and many studies contain major methodological flaws (Wardlaw 2001; Powers 2000; Kerr & Wardlaw 2000).

SUMMARY
The CT scan is the unquestioned ‘cardiogram of the brain’ (Buchan 2001). It is widely available, not very expensive, and applicable to the majority of stroke patients. It demonstrates haemorrhage immediately and, as far as we can tell, in all symptomatic patients. An established infarct is seen in around 50% of patients, but more often if the patient has a severe stroke. Early, subtle signs of infarction may be detected in patients scanned within six hours, and help to confirm the diagnosis of ischaemia. Although reliability is poor, these signs may reflect infarct pathology and could potentially be used to help select acute treatments. The major limitations of CT — poor imaging of the posterior fossa, less frequent detection of small infarcts, disappearance of haemorrhage after a week or two — are areas where MR is superior. The list of potential uses for MR in acute ischaemic stroke is expanding rapidly, but in the real world of clinical stroke medicine, we will likely have only clinical assessment and CT to guide us for some considerable time (Buchan 2001).

FOOTNOTE
Our Department of Clinical Neurosciences is currently studying the validity and reliability of early signs of infarction, using scans from the ECASS, ASK, MAST-I and IST-3 trials. Interested readers are encouraged to log onto the ACCESS website (Acute Cerebral CT Evaluation Stroke Study — http://thalia.dcn.ed.ac.uk) to improve their own CT interpretation skills.

REFERENCES


